

**MICROBIAL
TOXINS
IN
FOODS
AND
FEEDS**

*Cellular and Molecular
Modes of Action*

**Edited by
Albert E. Pohland,
Vulus R. Dowell, Jr.,
and
John L. Richard**

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Cellular and Molecular Modes of Action

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**On behalf of the UJNR, we dedicate the
proceedings of this symposium
to the memory of V. R. Dowell, Jr.**

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PREFACE

Although toxigenic fungi have been known since ancient times, modern mycotoxinology probably began with the early work of Joseph Forgacs and his colleagues in the 1950s. This science grew tremendously with the discovery of aflatoxins and aflatoxicoses in the early 1960s, particularly following the finding of the carcinogenicity of aflatoxins in test animal species. The discovery and identification of new mycotoxins and mycotoxins, development of analytical procedures, attempted measurement of human and animal exposure, evaluation of toxicological effects, estimation of risk due to human exposure, and development of regulatory control programs have been the major research goals over the past 30 years.

In recent years there has also been an explosive growth in our knowledge of the metabolites produced by the algae, especially the dinoflagellate-produced toxins, and the transmission of such toxins up the food chain to reef fish and shellfish. This knowledge has been invaluable in understanding and controlling human illness resulting from ingestion of seafood. We are now, for the first time, able to deal with such common seafood-related human diseases as paralytic, neurotoxic and amnesic shellfish and ciguatera poisoning.

The third, and perhaps most important area from a public health point of view, is the microbiological concern posed by the contamination of foods with bacterial pathogens and their toxic metabolites. Again, there has been impressive growth in our understanding of bacterial-related diseases in recent years. Also, the biotechnological advances in production, detection, and mode of action of microbial toxins was a major part of this area of research.

The U.S. Panel of the United States-Japan Cooperative Program on Development and Utilization of Natural Resources (UJNR) Joint Panels on Toxic Microorganisms decided that the area of microbial toxins had developed to a point that there was a need for a compilation of some of the latest information on the cellular and molecular modes of action of these toxins. It was felt that the best vehicle for exchange and dissemination of such information was an international symposium, with subsequent publication of the proceedings. Planning for the symposium began in early 1987, and with the cooperation of the Japanese panel in Tokyo in November 1987, the respective sections, topics and invited speakers were selected. This symposium and the resulting publication dealing with the cellular and molecular aspects of algal, bacterial and fungal toxins is the first of its kind. The speakers and contributors to the publication are to be commended for their willingness to participate and their timely submission of manuscripts.

The symposium was jointly sponsored by the U.S. and Japanese Panels on Toxic Microorganisms of the UJNR, the U.S. Department of Agriculture's

Agricultural Research Service, Food Safety and Inspection Service, and Office of International Cooperation and Development, and the Department of Health and Human Services, Public Health Service, Food and Drug Administration.

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UJNR PANEL ON TOXIC MICROORGANISMS

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INTRODUCTION

The UJNR (United States-Japan Cooperative Program on Natural Resources) was established in May, 1964, between Japan and the United States. The joint program of scientific and technical exchange on natural resources was a joint attack upon the environmental and resources problems that confronted both countries. As organized, each country had a coordinator, and areas of mutual interest between the two countries were established. Each area of interest was organized into a panel with a chairman and an alternate chairman on each side.

The original panels were:

- | | |
|--------------------|-------------------------|
| 1. Desalting | 5. Forage seeds |
| 2. Air pollution | 6. Water evaporation |
| 3. Water pollution | 7. Toxic microorganisms |
| 4. Energy | |

Initially, the Toxic Microorganism Panel had its emphasis on botulism with the title, Botulinum and other Toxic Microorganisms. At about this same time the fungal toxin, aflatoxin, was discovered; it and other fungal toxins shared equally with botulism.

In this paper Panel refers to the members of both the Japanese and United States Toxic Microorganisms Panels. In the beginning each side had seven members with C. R. Benjamin and Komei Miyaki as respective chairmen and Keishi Amano and C. W. Hesseltine as alternate chairmen. The Panel contained a mix of people who were experts on fungal mycotoxins and bacterial toxins.

Through the years the number of scientists has remained constant and with approximately an equal number of experts on bacterial and fungal toxins. The initial members of the Panel representing the United States, besides Benjamin and Hesseltine, were Keith Lewis, M. T. Bartram, John Graikoski, Carl Lamanna and Eugene Sporn. Representing the Japanese were the above named K. Miyaki and K. Amano along with K. Aibara, M. Kambayashi, H. Kurata, S. Matsuura, M. Nakano and S. Sakaguchi. Initially Sporn and Lamanna were consultants, and Matsuura was added at the first joint Panel meeting. Lamanna and Sporn had

been appointed as consultants because they were from the Defense Department, and there was some questions as to whether they could serve on the Panel as full members.

In establishing the membership of the panels, different departments were given the responsibility for organizing certain panels. The Panel on Toxic Microorganisms was assigned to Agriculture; hence Benjamin, who was research leader of the mycological investigations at Beltsville, was selected by the Department to be the chairman. He in turn selected Panel members with the approval of the appropriate department and the acceptance by the United States Coordinator, Dr. John C. Calhoun, from the Department of the Interior. The original Panel members came from the Departments of Agriculture, Interior, Defense, and Health, Education and Welfare as they had to come from government laboratories.

After establishment of the panels, the first U. S. meeting progress report on the UJNR was held on January 30, 1965. At this time each U. S. chairman prepared a report of his panel's progress. There were informal meetings on September 18, October 19 and January 9 preceding the January 30 report for the purpose of allowing the United States chairmen to discuss ways of cooperating with the Japanese chairmen. In his report of January 12, 1965, Benjamin stated that no U. S. Panel meeting had been held but that one was planned in February. He had been in contact with Dr. K. Miyaki, the Japanese Chairman in December, 1964 and at that time they had agreed that Panel activities should be focused upon botulism and mycotoxins, especially mycotoxins in rice and the aflatoxins. They agreed there should be an exchange of research papers on these two subjects.

The first concrete accomplishment was the supplying to the Japanese of a 300-page proceedings of a symposium on botulism and a list of current research projects in the United States on both types of toxins. In exchange, the Japanese Panel, with considerable effort, prepared and translated into English, "References on Botulism in Japan," in June, 1965. This contained the titles and short abstracts of some 90 Japanese papers. A similar bibliography consisting of 260 Japanese references on toxins produced by fungi was also supplied.

In the earliest report, Benjamin suggested areas of cooperation because no guidelines existed. Besides literature exchanges, he suggested an exchange of scientists, visits of panel members to each other's country, joint conferences and symposia. Later the members of the Panel decided there should be a statement of the Panel's activities and the microorganisms to be considered. This was put into a formal charter which reads as follows:

"The activities of the Toxic Micro-Organisms Panel are concerned with the pathogenic microorganisms and their toxins that contaminate foods and feeds. This contamination is a threat to the public health and causes unacceptable economic losses. The scope of Panel activities includes all aspects of these microorganisms--their distribution, the conditions of toxin production, their chemical characteristics, and the methods of control and prevention. Types of microorganisms specifically encompassed by this panel are toxic fungi, *Clostridium*, *Staphylococcus*, and *Vibrio parahaemolyticus*. This selection does not preclude future consideration of other microbial agents that produce food-borne diseases."

Joint Panel Meetings

The first joint meeting of the Panel was in June, 1966 in Tokyo with 4 American and all 6 of the Japanese members attending. The Japanese members came from the Ministry of Health and Welfare (3) and the Ministry of

Agriculture and Forestry (3). At this meeting the procedure of the joint Panel meetings was established. The first formal meeting was held between the two chairmen who discussed the week's program, agreed on a meeting procedure and location, arranged a study tour agenda (planned by the host panel), discussed the program for the scientific sessions, arranged special lectures and arranged for informal meetings. Many helpful suggestions were made by the U. S. Embassy staff. Besides the chairmen, all of the United States members as well as some of the Japanese members attended this first joint meeting.

The first day began with a formal meeting of the Panel with observers from the U. S. Embassy and the Japanese government in attendance. The coordinator for the Japanese UJNR panel, Dr. Y Shigihara, gave a formal speech that was translated into English. The U. S. Scientific Attache responded. The guest alternate chairman then served as moderator for the formal session with the host alternate chairman serving the second session. At these sessions members reported on pertinent research in Japan and the United States. At this time there was further exchange of reports, statistics and research papers. This included a list of 260 papers published in Japan on mycotoxins that had been translated, in part, into English.

The main business of this meeting was to engage in discussions on how best to effectively cooperate. Areas suggested were a symposium on toxic microorganisms to be held in 1968, exchange of young scientists between countries, joint projects, further literature exchange, and a second joint panel meeting in Washington, DC in 1967. The remainder of the week was devoted to site visits to laboratories of the host panel members and to giving special lectures, open to the public, on toxic microorganisms.

The 1966 joint Panel meeting was considered so successful by both countries that joint Panel meetings became a regular activity with meetings held in alternating countries. A typical joint Panel meeting began with a chairman to chairman meeting on Sunday afternoon or evening. Monday's session began with short talks by administrative people and by the two chairmen. Typically, moderators for the sessions were the alternative chairmen with the guest alternate chairman serving first. The remainder of the day and sometimes the next day was devoted to informal reports by each Panel member on the past year's development in his field, not only at his institute but information from other laboratories in his country. Each Panel member typically represented a special field. For example, on mycotoxins, one expert would be from his country's regulatory agency. Reprints of pertinent reports from both governments and private agencies as well as reports of poisoning outbreaks were exchanged among all panel members.

Also at these meetings, plans were made for the time, place and emphasis for the next meeting and included discussion of how to improve cooperation and future plans. Much valuable information was exchanged besides reports, such as, standards, samples and cultures. Considerable time was devoted to planning symposia and the publication of books on topics that had not been covered either by symposia or as books or reviews. The *Vibrio parahaemolyticus* symposium was a good sample because the Japanese were far ahead of the rest of the world in studies of this food poisoning bacterium.

After Dr. Okabe became chairman, the Joint Panel meetings spent less time on protocol items and more on scientific exchange. Since the time of his chairmanship the host panel, at considerable expense, had to furnish an interpreter which avoided many misunderstandings because none of the United States members understood or spoke Japanese, and some of the Japanese members were unfamiliar with spoken English. Typically the following day was a scientific session in which formal papers were presented. Usually outside experts from the host country in the field of toxic microorganisms were

invited to participate, and the whole meeting was open to the public, although there were never any formal announcements made.

One day was devoted to a scientific session on mycotoxins, and another to bacterial toxins. Although at first botulism was the only bacterial toxin considered, the program was soon broadened to include many others (at these scientific meetings copies or abstracts of the talks were made available). Typically, on Thursday and Friday study tours were conducted, sometimes with the entire guest panel going together. At other times the members went to separate places which included industrial research laboratories, government institutes, academic institutions and factories. These tours were useful because the host members made it possible to visit places not open to the public.

One interesting and useful procedure was seen in a food handling factory where one could not leave a rest room until both hands were put in a sanitizing liquid and a button pressed which unlocked a door to let you out.

The program was concluded either Friday or Saturday morning. Individual panel members usually made further arrangements to visit other institutions and specialists in their field. During these tours one or more of the panel members presented a lecture to the institute after the tour and discussions had ended. Table 1 is a listing of the types of places visited in the 1966 meeting in Japan.

This 1966 study tour was somewhat longer than usual because of the review of four projects supported by the United States involving the use of soybeans in foods.

Study tours in the United States were not as many, in part, because of the long distances between locations. They tended to be to university departments of microbiology and plant pathology, government research institutes, and to a lesser extent, to private or trade association laboratories. Among the two Panels, over a hundred study tours to various locations have taken place. To compensate for the greater numbers of sites visited in Japan, the United States Panel held their meetings in many different regions of the United States; thus, meetings were held in Washington, DC, Atlanta, Madison, Seattle, Texas A & M, New Orleans, Peoria, Ames, Orlando, and Bear River.

The Panel also evolved in the production of lengthy annual reports of the meeting and study tours. Also we tried to include in the Annual Report the accomplishments over the past year so that a record could be made to show our accomplishments. Some 22 separate reports have been prepared including one for 1987.

Exchange of Mutual Interest Items

This was a continuous activity of the Panel and often this occurred directly between individual researchers. Initially 150 cultures of toxin producing fungi were exchanged. In one instance 60 pounds of *Fusarium* contaminated grain containing vomitoxin was sent to Japan for evaluation. Mycotoxin standards of aflatoxin B₁ and M₁ were exchanged. Disease resistant stocks of peanuts including some which were rust resistant were compared. Standards of Type A botulinal toxin were sent to Japan and in exchange the United States received Type E botulinal toxin and Type E progenitor toxin. The Chiba Serum Institute has supplied the United States with a vial of Type E botulinal antitoxin. Type cultures of *Vibrio parahaemolyticus* were supplied to the United States. Another item exchanged was spectral data of some mycotoxins. Methods for mycotoxin detoxification of peanuts and corn were exchanged because the Japanese and the United States methods are different.